

PATENT

UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 10/820,486 Confirmation No. 7395
Applicant : Zhi-Jian Yu
Filed : 04/07/2004
TC/A.U. : 1616
Examiner : Brown, Courtney A.
Docket No. : 27529

Title: Cetylpyridinium Chloride as an Antimicrobial Agent in Ophthalmic Compositions

Declaration under 37 CFR §1.132

COMMISSIONER FOR PATENTS
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SIR:

I, Zhi-Jian Yu, Ph.D., hereby make the following declaration:

- 1 I received a Ph.D. in Physical Chemistry from Beijing University, China, in July, 1987.
- 2 From 9/87 – 5/89, I was a Postdoctoral Fellow at the INSTITUTE OF CHEMISTRY, ACADEMIA SINICA, Beijing, China.

- 3 From 6/89 – 5/94, I was a Postdoctoral Fellow in the Department of Chemical Engineering at AUBURN UNIVERSITY, Auburn, Alabama, researching the surface chemistry of solvent extraction of heavy metals.
- 4 Other professional positions prior to my current one are described in the C.V. attached hereto.
- 5 From 6/02 – Present, I have been employed as a Principal Scientist, ABBOTT MEDICAL OPTICS INC, Santa Ana, CA (formerly Advanced Medical Optics, Inc.), conducting research and development of products for dry eye treatment and contact lens cleaning and disinfection.
- 6 I have read the subject patent application, the rejections in the Office Action dated October 28, 2008, and the prior art cited against the invention: Tuse et al., (US 6,482,799), Araki et al. (US 2003/0203849), Zhao (US 2003/0228393), Dykens et al. (US 2003/0105167) and Huth (US 2004/0120916). I am fully familiar with the field of technology embraced by this patent application and the cited prior art.
- 7 The invention relates to an aqueous solution for contact lens care containing cetylpyridinium chloride (CPC) with an upper limit of about 9.5 ppm. When using CPC, it is critical to select the right surfactant or it will inactivate the antimicrobial activity. This Declaration shows that the non-ionic surfactant POP-POE is effective without reducing the antimicrobial properties of CPC. As a result, the amount of CPC in the solution can be surprisingly low.
- 8 Araki et al mentions that POP-POE block copolymers can function as gelling agents, among a group of cellulosic gelling agents, not surfactants. A person of

ordinary skill in the art would not focus on the POP-POE over the disclosed cellulosic gelling agents, for purposes of the present invention.

9 POP-POE as used in the present invention is significantly below the level that would be required to 'gel'. In fact, we would like to avoid 'gelling' completely. As such, one of ordinary skill in the art would not have looked at the teaching of Araki to formulate a multi-purpose contact lens solution.

10 At gelling concentrations, this would have taught away from the formulation of a MPS. Gelling occurs at very high POP-PEO concentration. For example, the viscosity of a 10% w/v Pluronic F87 solution is only 4 cps. The viscosity of 10% Tetronic 904 is 2.66 cps. That is, both solutions are watery. A gelling solution normally has a viscosity of more than 100 - 10,000cps. Therefore, > 10% w/v of POP-PEO is required as a gelling agent.

11 POP-POE as a gelling agent has several problems.

i. Inactivation of CPC antimicrobial activity due to too high POP-PEO concentration. This can also be seen from Table 4. When Pluronic F87 increases from a detergent level of 0.05% to 0.2%, the AME activity decreases to a marginal level as a stand-alone MPS. At the POP-PEO concentration of > 10%, CPC will be inactive as a disinfecting agent.

ii. It will excessively increase the retention time of CPC on the cornea due to the composition's high viscosity, which would hold the CPC in place over the cornea, causing Corneal toxicity such as cornea staining and irritation.

iii. When the composition is evaporated during normal usage, a thick film would form in the lens case causing microbes to be trapped underneath the film and separated from the disinfecting solution.

iv. Any gel residue left on a contact lens (it is standard for MPS residue to be left on the lens when it is inserted in the eye) would be too irritating and cytotoxic.


12 The table below contains the results of comparative experiments conducted as described on pages 21 – 25 of the specification. One can see that CPC/POP-POE has greater antimicrobial efficacy than CPC with other surfactants. Pluronic F87 and Tetronic 904 are PPO-PEO surfactants, and cause no noticeable loss in the antimicrobial activity of CPC at the tested concentration. In fact, Pluronic F87 and Tetronic 904 enhanced the activity against *C. albicans* 10231 when compared with no surfactant in solution (although I expect it to decrease above 1% w/w). In contrast, TPGS, Tween 80 and Cremophor-40, which are non-PPO-PEO surfactants, caused almost total loss in antibacterial efficacy.

	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w
TPGS	0.10					
Tween 80	0.10					
Cremophor 40	0.10					
Pluronic F87	0.10					
Tetronic 904	0.10					
CPC	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004
Boric acid	0.60	0.60	0.60	0.60	0.60	0.60
Sodium Borate-10H ₂ O	0.15	0.15	0.15	0.15	0.15	0.15
NaCl	0.45	0.45	0.45	0.45	0.45	0.45
EDTA	0.05	0.05	0.05	0.05	0.05	0.05
	Log drops @ 6 hours					
<i>S. marcescens</i> 13880	>4.38	0.15	-0.01	0.07	>4.38	>4.38
<i>S. aureus</i> 6358	>4.42	0.11	0	0.1	>4.42	>4.42

<i>P.aeruginosa</i> 9027	>4.3	1.3	0.2	0.2	>4.3	>4.3
<i>C. albicans</i> 10231	2.8	0	-0.1	-0.2	>4.1	>4.1
<i>F.solani</i> 30361	>4.0	0.2	0.3	0.4	>4.0	>4.0

13 I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 03/30/09

By: 
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EXPERIENCE

6/02 – Present ABBOTT MEDICAL OPTICS INC, Santa Ana, CA

Principal Scientist

- Conduct research and development of products for dry eye treatment and contact lens cleaning and disinfection.

11/97 – 6/02 METREX RESEARCH CORPORATION, Orange, CA

Senior Research Scientist

- Developed **Caviwipes®** and **Metriwipes®** for hard surface disinfection.
- Developed **Compliance™**, a high level disinfectant and sterilant for medical instruments
- Developed **Metrilube®**, **Metriwash®**, and **EmPower™** for medical instrument pre-cleaning.

8/96 – 11/97 CUBIST PHARMACEUTICALS INC., Cambridge, MA

Research Scientist

- Designed and formulated new generation antibiotics for MRSA and VRE.
- Developed long-lasting aerosol formulations for respiratory tract infection treatment..
- Developed I.V. injectable formulation for water insoluble antibiotics using cyclodextrins as drug carriers.

3/95 – 7/96 ALLERGAN INC., Irvine, CA

Research Scientist

- Conducted ophthalmic product development for dry eye treatment.

5/94 – 3/95 NYCOMED SALUTAR INC., Sunnyvale, CA

Research Scientist

- Researched drug encapsulation, and nano-particle coating and developed parenteral diagnostic imaging drugs.

6/89 – 5/94 AUBURN UNIVERSITY, Auburn, Alabama
Department of Chemical Engineering

Postdoctoral Fellow

- Researched the surface chemistry of solvent extraction of heavy metals.

9/87 – 5/89 **INSTITUTE OF CHEMISTRY, ACADEMIA SINICA, Beijing, China**

Postdoctoral Fellow

- Researched static and time resolved fluorescence in surfactant solutions.

EDUCATION Ph.D. Physical Chemistry, Beijing University, China, July, 1987.

MS. Physical Chemistry, Beijing University, China, July, 1984.

BS. Chemistry, Beijing University, China, April, 1982.

HONORS 1988 Distinguished Young Chemist Award by Chinese Chemical Society and Chinese National Science Foundation.

PATENTS

1. **Zhi-Jian Yu**, ALKYLAMINE AS AN ANTIMICROBIAL AGENT IN OPHTHALMIC COMPOSITIONS, US7,488,706B2.
2. **Zhi-Jian Yu**, ALKYLAMINE AS AN ANTIMICROBIAL AGENT IN OPHTHALMIC COMPOSITIONS, US7,157,412 B2.
3. Robert Glick, Stanley Huth, **Zhi-Jian Yu**, and Charles Powell, Compositions and Methods Using Sub-ppm Combinations of Polyquaternium-1 and High Molecular Weight PHMB, US7,105,473.
4. Robert Glick, Stanley Huth, **Zhi-Jian Yu**, and Charles Powell, Compositions and Methods Using Sub-ppm Combinations of Polyquaternium-1 and High Molecular Weight PHMB, US6,930,077.
5. **Zhi-Jian Yu** and Stan Huth, Cleaning and Decontaminating Dialyzers by Per-compound Solutions, US6,468,472.
6. Stan Huth and **Zhi-Jian Yu**, Simultaneous Cleaning and Decontaminating Compositions and Methods. US6,448,062.

PUBLICATIONS

1. Zhi-Jian Yu, Diane Croner, Stan Huth and Ophelia Panganiban, "Wettability of Contact Lenses" Review of Cornea & Contact Lenses, June, 42-47, 2006.

2. Lauren Crawford, David Tobia, Stanley Huth, **Zhi-Jian Yu**, Tina Yu, "Factors to Consider When Selecting an Aldehyde-Based High-Level Disinfectant" Managing Infection Control, May, 78-80, 2003.
3. Lauren Crawford, **Zhi-Jian Yu**, Erin Keegan, Tina Yu, "Comparison of Commonly Used Surface Disinfectants, Oral Health, March 2001.
4. Lauren Crawford, **Zhi-Jian Yu**, Erin Keegan, Tina Yu, "A comparison of Commonly Used Surface Disinfectants, Alcohol-, Phenol-, Chlorine-, and Quaternary Amine-Based Disinfectants" Infection Control Today, November, 24 -28, 2000.
5. **Zhi-Jian Yu**, Ibrahim, Taleb H., R.D. Neuman, "Aggregation Behavior of Cobalt (II), Nickel (II), and Copper (II) Bis(2-ethylhexyl) Phosphate Complexes in n-Heptane" Solvent Extraction and Ion Exchange, 16, 1437-1463, 1998.
6. Naifu Zhou, Jinguang Wu, **Zhi-Jian Yu**, R.D. Neuman, Dujin Wang and Guangxian Xu "Investigation of Aggregation in Solvent Extraction of Lanthanides by Acidic extractants," Sci. China, Ser. B: Chem., 40, 61-71, 1997.
7. Naifu Zhou and **Zhi-Jian Yu**, "Solution Aggregation Structures Formed by Rare Earth Ions and Acidic Extractants in Solvent Extraction," Sci. China, Ser. B: Chem., 27, 235-256, 1997
8. **Zhi-Jian Yu** and R.D. Neuman, "Properties and Structures of Sodium and Transition Metal Salts of Bis(2-Ethylhexyl) Phosphate/n-Heptane and the Effect of Water" in «DYNAMIC PROPERTIES OF INTERFACES AND ASSOCIATE STRUCTURES», Shah, D.O., Ed., AOCS Press Publ., Champaign, IL, 1996, p.166-182.
9. R.D., Neuman. **Zhi-Jian Yu** and T. Ibrahim, "Role of Reversed Micelles of Acidic Organo Phosphorus extractants in Cobalt/Nicole separation - a Position Paper," in «VALUE ADDING THROUGH SOLVENT EXTRACTION, PROC. INTERN. SOLVENT EXTRACTION CONF., ISEC 96», D.C. Shallcross, R.Paimin and L.M. Prvcic, Eds., the University of Melbourne, Parkville, 1996, p.135-140, Australia.
10. **Zhi-Jian Yu** and R.D. Neuman, "Reversed Micellar Solution-to-Bicontinuous Microemulsions Transition in Sodium Bis(2-Ethylhexyl) Phosphate/n-Heptane/Water System" Langmuir, 11, 1081-6, 1995.
11. R.D., Neuman. **Zhi-Jian Yu** and T. Ibrahim, "Microscopic Interfaces in Solvent Extraction," International Chemical Conference of Pacific Basin Society, Honolulu, Hawaii, December, 1995.
12. **Zhi-Jian Yu** and R.D. Neuman, "Giant Rodlike Reversed Micelles Formed by Sodium Di(2-Ethylhexyl) Phosphate in n-Heptane" Langmuir, 10, 2553-8 (1994).

13. **Zhi-Jian Yu** and Ronald D. Neuman, "Giant Rodlike Reversed Micelles and Bicontinuous Microemulsion in Sodium Di(2-Ethylhexyl) Phosphate/n-Heptane/Water System", 68th Colloid and Surface Science Symposium, Stanford University, Stanford, California, June 19, 1994.
14. **Zhi-Jian Yu** and R.D. Neuman, "Non-Critical Behavior Near the Cloud Point in Perfluorinated Ionic Micellar Solution", Langmuir, 10, 377, 1994.
15. **Zhi-Jian Yu** and R.D. Neuman, "Giant Rodlike Reversed Micelles" Journal of American Chemical Society, 83, 10, 1994.
16. **Zhi-Jian Yu** and Ronald D. Neuman, "Properties and Structures of Sodium and Transition Metal Salts of Bis(2-Ethylhexyl) Phosphate in n-Heptane and the Effect of Water", 85th AOCS Annual Meeting & Expo, May 8, 1994, Atlanta, Georgia.
17. **Zhi-Jian Yu** and G.-X. Zhao, "Micellar Compositions in Mixed Surfactant Solutions", Journal of Colloid and Interface Science, 156, 325, 1993.
18. R.D. Neuman, S.J. Park, N.F. Zhou, **Zhi-Jian Yu** and P. Shah, "Interfacial Phenomena in Hydrometallurgical Solvent Extraction Systems", Eighth Symposium on Separation Science and Technology for Energy Applications, Oct. 25, 1993, Oak Ridge, Tennessee.
19. **Zhi-Jian Yu**, N.-F. Zhou and R.D. Neuman, "The Role of Water in the Formation of Reversed Micelles: an Anti-Micellization Agent", Langmuir, 8, 1885, 1992.
20. **Zhi-Jian Yu** and R.D. Neuman, "Light-Scattering Measurements of Surfactant Solutions", Langmuir, 8, 2074, 1992.
21. **Zhi-Jian Yu** and Ronald D. Neuman, "Solution Properties of Mixtures of Alkylammonium Bromide and Sodium Perfluorooctanoate," 8th International Symposium on Surfactants in Solution, June 10, 1990, Gainesville, FL.
22. **Zhi-Jian Yu**, X. Zhang, G. Xu and G.-X. Zhao, "Physicochemical Properties of Aqueous Mixtures of Tetrabutylammonium Bromide and Anionic Surfactants. 3. Effects of Surfactant Chain Length and Salinity," Journal of Physical Chemistry, 94, 3675, 1990.
23. J. Wu, F. Liu, **Zhi-Jian Yu**, N.-F. Zhou and R.D. Neuman, "W/O Microemulsions Formed by Acidic Extractants and Effect of Lanthanides," Proc. Intern. Solvent Extraction Conf., ISEC 90, p.195 - 200, 1990, Kyoto.
24. **Zhi-Jian Yu**, Z. Zhou and G. Xu, "Physicochemical Properties of Aqueous Mixtures of Tetrabutylammonium Bromide and Anionic Surfactants. 2. Micellar Growth Patterns and the Effect of Intermicellar Interactions on Light-Scattering Data," Journal of Physical Chemistry, 93, 7446-51, 1989.

25. **Zhi-Jian Yu** and G. Xu, "Physicochemical Properties of Aqueous Mixtures of Tetrabutylammonium Bromide and Anionic Surfactants. 1. Temperature-Induced Micellar Growth and Cloud Point Phenomenon," Journal of Physical Chemistry, **93**, 7441-5, 1989.
26. **Zhi-Jian Yu** and G.-X. Zhao, "Physicochemical Properties of Aqueous Mixtures of Cationic-Anionic Surfactants. II. Micelle Growth Pattern of Equimolar Mixtures," Journal of Colloid and Interface Science, **130**, 421-31, 1989.
27. **Zhi-Jian Yu** and G.-X. Zhao, "Physicochemical Properties of Aqueous Mixtures of Cationic-Anionic Surfactants. I. The Effect of Chain Length Symmetry," Journal of Colloid and Interface Science, **130**, 414-20, 1989.
28. **Zhi-Jian Yu**, X. Zhang and G. Xu, "Study of Solubilization of Pyrene in Perfluorooctanoate Micelles," Acta Physico Chimica Sinica, **5**, 723, 1989.
29. Z. Zhou and **Zhi-Jian Yu**, "Investigation on Micellar Growth in Aqueous Tetradecyl pyridium Bromide Solutions Using Photon Correlation Spectroscopy," Acta Physico Chimica Sinica, **1**, 141-53, 1985.